

# iVIEW

EDITOR'S PAGE

## The Myth of the Mild Vulnerable Plaques

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Few core concepts introduced in the past several decades have become more ingrained in the psyche of the cardiologist such as the belief that coronary occlusion and myocardial infarction most frequently evolve from a mildly stenotic coronary artery disease (1). This perception owes its origin to the observations made 25 years ago that among patients in whom coronary angiography had been performed at some point, days to years before a myocardial infarction, the lesion responsible for the subsequent infarct was angiographically less than severe in the majority of cases (2,3). Over the years, this hypothesis has been supported by other angiographic studies, most convincingly from the National Heart, Lung, and Blood Institute's Dynamic Registry (4), the PROSPECT (Predictors of Response to Cardiac Resynchronization Therapy) trial (5), and the COURAGE (Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation) trial (6), although notably challenged by CASS (Coronary Artery Surgery Study) (7). However, all these studies do not take into account the interval progression of lesion severity that may occur before coronary thrombosis. Angiographic studies performed during a myocardial infarction purporting to reveal underlying plaque severity after thrombolysis (8) or aspiration (9) are less compelling given the inability of these modalities to completely remove thrombus. Although fraught with selection bias, a pathologic study of patients recently dying after myocardial infarction or sudden cardiac death has suggested that the fateful plaques were almost always at least moderately occlusive and that the vulnerable plaques probably expanded in size before they ruptured (10). PROSPECT (5), which relied on intravascular imaging rather than angiography, suggested that the lesions responsible for future

acute coronary syndromes (ACS) were indeed not mild but rather were in all cases moderate or severe.

In this issue of *iJACC*, we posed the question "Are the culprit lesions severely stenotic?" and received 2 diametrically opposed opinions from Niccoli et al. (No!), and Ambrose and Berg (Yes!) (11). Both groups buttress their positions with detailed data from studies correlating imaging results with clinical end points. Each treatise also discusses the limitations of the published studies. Thus, how can we reconcile these conflicting results? Or are both positions correct (and if so, how is this possible)? The answer lies in understanding the limitations of coronary angiography as an imaging method (12). First, the angiogram is in fact a "luminogram," incapable of revealing plaque that resides in the vascular tunica media and adventitia that does not narrow the inner diameter of the coronary vessel (13). This is particularly relevant because plaque accumulation results in vessel expansion before luminal compromise (14). This compensatory mechanism is usually overcome when the plaque occupies approximately 40% of cross-sectional vascular area (or plaque burden), with progressive atherosclerosis thereafter resulting in luminal encroachment. Thus, by the time a lesion in a coronary artery with a 3.0-mm reference vessel diameter appears angiographically mild (e.g., 33% diameter stenosis), the external elastic membrane of the vessel may have swollen to 5.5 mm or greater, and the plaque burden may in truth be >85%. Indeed, the fact that coronary angiography can markedly underestimate the pathologic degree of atherosclerosis was elegantly demonstrated 40 years ago (15). Second, the angiogram is a 2-dimensional representation of a complex 3-dimensional structure. Given plaque eccentricity (which is the rule rather than the exception), angiography may either overestimate or underestimate the true cross-sectional lesion severity, depending on the incident angle of the x-ray beam as it transects the narrowed lumen (10,13). For all of these reasons, the angiogram is a gold standard, which we should not rely upon for lesion analysis. In this regard, tomographic

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imaging techniques are more accurate, using pathology as a gold standard (10).

When trying to weigh the strength of data from conflicting sources, the strongest evidence usually resides in prospective studies formulated to answer the issue in question. In this regard, the multicenter PROSPECT study was designed to overcome the limitations of prior studies, prospectively enrolling 697 patients in whom angiography and 3-vessel intravascular imaging with grayscale and radio-frequency ultrasound was performed to characterize those untreated nonculprit lesions responsible for future ACS events (5). With median follow-up of 3.4 years, the strongest predictor of future events was the intravascular ultrasound (IVUS)-derived plaque burden at the nonculprit lesion. The per lesion event rate was 9.5% for the 298 untreated lesions in which plaque burden was  $\geq 70\%$ , 2.5% for the 798 lesions in which plaque burden was  $\geq 60\%$  to  $70\%$ , and  $<0.5\%$  for thousands of lesions with  $<60\%$  plaque burden (16). Indeed, not a single adverse event arose from a segment of the coronary tree with  $<40\%$  plaque burden. The minimal luminal area was also an independent predictor of future ACS events. And given the space occupying nature of the measuring catheter, IVUS may underestimate the true severity of lesions with the greatest luminal narrowing. Of note, although lesions destined to cause future ACS were severe by IVUS, by quantitative coronary angiography, the mean angiographic diameter stenosis of these lesions was only 32.3%, although they did progress to 65.4% at the time of the future event, consistent with rapid lesion progression due to plaque rupture and/or coronary thrombosis. The fact that plaque burden was the most powerful predictor of future ACS

events was subsequently confirmed in the single-center prospective VIVA (VH-IVUS in Vulnerable Atherosclerosis) study, which was of similar design as PROSPECT (17). The information available from the analyses of pathological specimens that compared the vulnerable plaques and ruptured plaques demonstrated that the plaque burden was substantially higher in the latter; this indirectly suggested that the plaques expand further before rupture.

PROSPECT (and VIVA) have thus demonstrated that lesions responsible for future major adverse cardiac events are both mild and severe: mild by angiography (as defined by the luminal diameter stenosis relative to the adjacent reference lumens) but severe by IVUS (as defined by large atheroma volume with severe cross-sectional area narrowing), the latter more accurately reflecting the truth. These studies have also suggested that the lesions must further expand during the interval between the initial assessment of vulnerable lesion and the subsequent event (10). This is mechanistically credible, because studies have reported that the greater the volume of atheroma, the greater the burden of lipid and necrotic core, the thinner the fibrous cap, the more severe the inflammation, the more deranged the vaso vasorum, and the more abnormal the stress-strain relationships (18,19). Should we then bury the myth that vulnerable plaques are mild—and stop relying on coronary angiography for sophisticated lesion analysis?

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